REMARKS

The claims are not amended with this paper. Currently pending in the application are claims 1, 7-9, 14, 15, 19-22 and 27-29.

Rejections Under 35 U.S.C. § 103

(i) Claims 1, 9, 14, 15, 19-22, and 27 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over United States Patent No. 5,589,480 to Elkhoury, *et al.* ("Elkhoury"), in view of United States Patent No. 5,849,761 to Yaksh ("Yaksh"), United States Patent No. 5,840,731 to Mayer, *et al.* ("Mayer"), United States Patent No. 5,635,204 to Gervitz, *et al.* ("Gervitz") and T. Lin, *et al. Can. J. Anesth.* Feb. 1998, 45(2), pages 175-177 ("Lin"). Applicants respectfully disagree and traverse.

To properly determine a *prima facie* case of obviousness, the Examiner "must step backward in time and into the shoes worn by the hypothetical 'person of ordinary skill in the art' when the invention was unknown and just before it was made." M.P.E.P § 2142. This is important, as "impermissible hindsight must be avoided and the legal conclusion must be gleaned from the prior art." *Id.* Although Applicants do not agree that the references cited in the Office Action, "Knowledge in the prior art of every element of a patent claim ... is not of itself sufficient to render the claim obvious." *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966); *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1333-34 (Fed. Cir. 2002).

The claimed invention provides topical pharmaceutical compositions and methods of providing analgesia comprising morphine and a tolerance-attenuating dosage of ketamine sufficient to yield a dose-lowering effect on morphine.

The Office Action alleges that Elkhoury teaches a topical composition of morphine that provides an analgesic effect in a localized area without migration to the bloodstream. Elkhoury does not teach a topical pharmaceutical composition comprising a combination of morphine and ketamine, let alone a tolerance-attenuating dosage of ketamine sufficient to yield a dose-lowering effect on morphine. Elkhoury also does not teach or suggest the use of topical compositions for effectively delivering ketamine and

morphine to local peripheral receptors and not to central receptors, as required by the pending claims.

The Office Action relies on Yaksh, Mayer, Gervitz and Lin to rectify the deficiencies of Elkhoury. In particular, the Office Action alleges that: Yaksh teaches the use of low dosages of morphine to avoid CNS side effects; Mayer teaches the addition of ketamine to enhance analgesia and/or reduce side effects; Gervitz teaches the use of ketamine for topical administration; and Lin teaches the combination of ketamine, morphine and bupivacaine.

These assertions in the Office Action appear to rely on impermissible hind-sight, using the present specification as a blueprint to reconstruct the claimed invention from the isolated teachings of the prior art. Indeed, the Examiner has chosen discrete disclosures from each of the **four** supplementary references – in some instances a single sentence taken out of context – to arrive at his conclusion without demonstrating where in each reference the motivation to combine the reference with the primary reference, let alone with the other supplementary references, is taught. Applicants respectfully point out that hind-sight analysis is improper. See, e.g., *Grain Processing Corp. v. American Maize-Prods. Co.*, 840 F.2d 902, 907, 5 USPQ2d 1788, 1792 (Fed. Cir. 1988). Applicants further contend that none of the cited references, alone or in combination, can "bridge the gap" between the teachings of Elkhoury and the subject matter of the pending claims.

With regard to Yaksh, the Office Action concedes that Yaksh teaches the disadvantage of the use of morphine in that it is taught to have short duration of activity and to have systemic and CNS side effects when used at high levels. (See, Office Action – Paragraph 8). Applicants respectfully submit that Yaksh teaches away from the use of morphine at all. Indeed, Yaksh states that "other opioids, such as morphine, that readily cross the blood brain barrier could be effective as anti-hyperalgesics, but their permeability through the blood brain barrier results in abuse liability" (Column 4, lines 45-49) and that "the compositions provided herein, contain opioids that ***do not,*** upon topical or local administration, substantially ***cross the blood brain barrier***..." (Column, 4, lines 50-53). Furthermore, Yaksh does not teach or suggest the use of

topical compositions for effectively delivering ketamine and morphine to local peripheral receptors and not to central receptors, as required by the pending claims. In view of these teachings (or lack thereof), one of ordinary skill in the art would have lacked the motivation to combine Yaksh with Elkhoury to arrive at the claimed invention.

With regard to Mayer, the Office Action alleges that Mayer teaches that the analgesic effectiveness of a combination drug composition comprising at least one analgesic (for example, morphine) is significantly enhanced by the addition of an NMDA receptor antagonist (for example, ketamine). It is important to note that Mayer is limited to the discussion of compositions comprising both an analgesic (either opioid or non-opioid) and a second component chosen from a sedative, a muscle relaxant or a non-opioid analgesic. Moreover, Mayer does not disclose the use of topical compositions for effectively delivering ketamine and morphine to local peripheral receptors and not to central receptors, as required by the pending claims. Accordingly, one of ordinary skill in the art would not appreciate, based on a reading of Mayer, that morphine could be administered concurrently with a tolerance-attenuating dose of a ketamine, to local peripheral receptors, to attenuate, reverse, or prevent tolerance to analgesics.

With regard to Gervitz, although the Office Action alleges that Gervitz teaches the use of ketamine for topical administration, Applicants contend that Gervitz is directed to a method of inducing surgical anesthesia via transdermal administration of an amnesia-producing drug and, subsequently, an anesthesia-producing drug. Applicants submit that the transdermal administration according to Gervitz would result in a central (systemic) effect, not a local (peripheral) effect. Gervitz does not, however, disclose a tolerance-attenuating dose of ketamine when administered in combination with morphine. In fact, Gervitz neither teaches nor suggests tolerance attenuation or the need therefor. Accordingly, one of ordinary skill in the art would not appreciate, based on a reading of Gervitz, that morphine could be administered concurrently with a tolerance-attenuating dose of a ketamine to attenuate, reverse, or prevent tolerance to analgesics. Furthermore, one of ordinary skill in the art would not understand Gervitz to teach or suggest the use of topical compositions for effectively delivering ketamine and

morphine to local peripheral receptors and not to central receptors, as required by the pending claims.

With regard to Lin, the Office Action alleges that Lin teaches that it is well known in the art that an NMDA receptor antagonist can abolish nociceptor hypersensitivity. As Applicants understand the reference, Lin describes the use of spinal (i.e., central) delivery of certain compositions. Lin does not teach or suggest the use of topical compositions for effectively delivering ketamine and morphine to local peripheral receptors and not to central receptors, as required by the pending claims.

None of Elkhoury, Yaksh, Mayer, Gervitz and Lin alone, or in combination, teaches or suggests topical pharmaceutical compositions for effectively delivering ketamine and morphine to local peripheral receptors and not to central receptors, as required by the pending claims, nor methods of providing analgesia comprising morphine and a tolerance-attenuating dosage of ketamine sufficient to yield a dose-lowering effect on morphine, wherein the morphine and ketamine function through local peripheral receptors and not central receptors, as required by the pending claims.

Applicants submit that none of the references cited in the Office Action teaches or suggests that the interaction between NMDA receptors and opiates occurs peripherally. Thus, there would be no expectation that a tolerance-attenuating amount of ketamine could be delivered to local peripheral receptors and have a dose-lowering effect on the morphine, as recited by the present claims. It would therefore not have been obvious for the skilled artisan to combine the teachings of the cited references as stated in the Office Action, nor would one of ordinary skill in the art be motivated to modify the teachings of Elkhoury in light of Yaksh, Mayer, Gervitz and Lin to arrive at the claimed invention. Furthermore, one of ordinary skill would not have had a reasonable expectation that topical pharmaceutical compositions for effectively delivering ketamine and morphine to local peripheral receptors and not to central receptors would have a dose-lowering effect on the morphine.

For at least the foregoing reasons, reconsideration and withdrawal of the rejection is proper and such action is respectfully requested.

(ii) Claims 7, 8, 28, and 29 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Elkhoury, Yaksh, Mayer, Gervitz and Lin, in further view of United States Patent No. 5,322,683 to Mackles et al. ("Mackles").

As discussed above, none of Elkhoury, Yaksh, Mayer, Gervitz and Lin alone, or in combination, teach or suggest topical pharmaceutical compositions and methods of providing analgesia by effectively delivering ketamine and morphine to local peripheral receptors and not to central receptors, to yield a dose-lowering effect on morphine, as required by the pending claims.

In regard to Mackles, the Office Action alleges that Mackles teaches that lidocaine is a topical analgesic. Mackles does not teach or suggest the use of lidocaine in combination with any other active ingredients, let alone morphine and a tolerance-attenuating dosage of ketamine sufficient to yield a dose-lowering effect on morphine. Mackles does not teach or suggest the use of topical compositions for effectively delivering ketamine and morphine to local peripheral receptors and not to central receptors, as required by the pending claims. In short, Mackles does not remedy the deficiencies of the other references discussed above, and cannot render obvious claims 7, 8, 28, and 29. Accordingly, reconsideration and withdrawal of the rejection to claims 7, 8, 28, and 29 under 35 U.S.C. § 103 is respectfully requested.

Double Patenting Rejections

Claims 1, 7-9, 14, 15, 19-22 and 27-29 stand rejected on the grounds of nonstatutory obviousness-type double patenting over claims 2 and 11-15 of United States Patent No. 6,825,203. Claims 1, 9, 14, 15, 19-22 and 27 further stand provisionally rejected on the grounds of nonstatutory obviousness-type double patenting over claims 27-35 of copending U.S. Application Serial No. 10/823,365.

It still remains unknown what subject matter claimed and disclosed in the present application will be deemed allowable. Therefore, Applicants respectfully traverse these rejections, and maintain the request that these rejections be held in abeyance until subject matter is deemed allowable in this application.

CONCLUSION

Applicant believes the pending application is in condition for allowance. Early and favorable action is earnestly requested.

Applicants conditionally petition for any extension of time necessary for consideration of this response. The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 04-1105, under Order No. 62072 (51590).

Respectfully submitted,

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